THOMAS O. HENTELEFF
RICHARD S. MOREY
KINSEY S. REAGAN
PETER R. MATHERS
ANTHONY L. YOUNG
ANNE V. MAHER
BONNIE A. BEAVERS
DANIEL R. DWYER
GLENN E. DAVIS
STACY L. EHRLICH
JENNIFER A. DAVIDSON
STACEY L. VALERIO
JONATHAN M. WEINRIEB
CARRIE C. HORN

OF COUNSEL:
WILLIAM J. HARDY

LAW OFFICES
KLEINFELD, KAPLAN AND BECKER, LLP
1140 NINETEENTH STREET, N.W.
WASHINGTON, D. C. 20036-6606
TELEPHONE (202) 223-5120
FACSIMILE (202) 223-5619
www.kkblaw.com

WEST COAST OFFICE:
ONE MARKET STREET
STEUART TOWER, SUITE 1450
SAN FRANCISCO, CA 94105-1313
TELEPHONE (415) 538-0014
FACSIMILE (415) 538-0016

VINCENT A. KLEINFELD
1907-1993

ALAN H. KAPLAN
1930-2001

February 13, 2007

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

SUPPLEMENTAL SUBMISSION IN SUPPORT OF CITIZEN PETITION AND PETITION FOR STAY
DOCKET NOS. 2004P-0140/CP1 AND 2004P-0140/PSA 1

On behalf of King Pharmaceuticals, Inc. ("King"), the undersigned hereby make this supplemental submission in support of the above referenced Citizen Petition and Petition for Stay ("the King Petitions") to request that the Commissioner of Food and Drugs ("the Commissioner") take the actions requested below.

ACTION REQUESTED

The Commissioner is requested to: (a) prohibit the removal from generic metaxalone labeling of any information that appears in the new Skelaxin® (metaxalone) ("Skelaxin") labeling and (b) require applicants seeking approval to market generic metaxalone products that rely on Skelaxin as the reference listed drug ("RLD") to submit a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) to United States Patent Nos. 6,407,128 ("the '128 patent") and 6,683,102 ("the '102 patent").

STATEMENT OF GROUNDS

The recent approval by the United States Food and Drug Administration ("FDA") of revised labeling for Skelaxin, which discusses in detail the significant food effects and related age and gender effects discovered through at least five clinical studies, as well as a meta-analysis of those studies, underscores the King Petitions and effectively supersedes previous consideration by the FDA of a carve-out of food effect information and the submission of a related statement under 21 U.S.C. § 355(j)(2)(A)(viii) ("section viii statement"). In this supplemental submission, King explains the significance of the recent FDA approval of new Skelaxin labeling and the basis on which this matter should be resolved.

I. FACTUAL BACKGROUND

For the convenience of the Commissioner, a brief summary of the King Petitions and related actions is provided below.

A. The Prior Submissions

The King Petitions were originally submitted in response to the March 1, 2004 "Dear Applicant" Letter issued by the Director of the Office of Generic Drugs ("OGD") ("the March 1, 2004 Letter") regarding metaxalone labeling, which, in a reversal from the FDA's previous position, stated that applicants seeking approval to market generic versions of Skelaxin might omit from their labeling certain pharmacokinetics information present in the then-current version

of Skelaxin labeling. Furthermore, the March 1, 2004 Letter stated that if such applicants decided to take advantage of a carve-out, they must submit section viii statements in lieu of a certification under 21 U.S.C. § 355(j)(2)(A)(vii) with respect to the '128 patent. The King Petitions requested that the FDA prohibit the removal from generic metaxalone labeling of the pharmacokinetics information appearing in the then-current Skelaxin labeling and require generic metaxalone applicants to certify to the King '128 patent. Specifically, the King Petitions demonstrated that removal of the pharmacokinetics information would render generic metaxalone products less safe and effective than Skelaxin.[1] Furthermore, the King Petitions requested that FDA stay approval of any generic metaxalone products until the FDA has fully evaluated and ruled on the King Petitions.

On January 28, 2003, Eon Labs, Inc. ("Eon") filed a Citizen Petition with FDA (Docket No. 03P-0027) requesting that FDA amend the Skelaxin labeling to include language from a never-implemented May 31, 2002 approval letter that was corrected on June 20, 2002 or, in the alternative, to determine that the May 31, 2002 labeling was not withdrawn for safety or effectiveness reasons. Given the recent approval of new Skelaxin labeling, that petition is now moot.

On April 5, 2004, Mutual Pharmaceutical Co., Inc. ("Mutual") filed a Petition for Stay (Docket No. 04P-0140/PSA2) opposing the King Petitions and requesting that FDA stay

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[1] King made this demonstration despite the fact that generic applicants have the burden of proving that omission of information would not cause a generic product to be less safe and effective than the RLD. *See* King Citizen Pet. at 27 (March 18, 2004); King Supplemental Submission at 28 (July 21, 2004).

approval of King's pending labeling supplement seeking revision of the Skelaxin labeling. On December 8, 2005, Mutual withdrew its Petition for Stay and related submissions and submitted to the FDA data from three studies that indicate that "the metaxalone food-effect may in fact have important, clinically significant consequences for the safe administration of metaxalone."

B. The Recent Revision of the Skelaxin Label

Because Skelaxin was originally approved prior to enactment of the Drug Amendments of 1963, clinical studies relating to absorption, distribution, metabolism, and excretion ("ADME"), which are commonplace today, did not exist. Over the last few years, however, King, Elan Pharmaceuticals, Inc. ("Elan"), and Mutual have performed a series of pharmacokinetic studies that have shed light on the ADME qualities of metaxalone. The first of these studies was performed by Mutual and resulted in the FDA reclassifying Skelaxin as a drug product for which potential or actual bioequivalence problems exist ("bio-problem drug"), which is now reflected in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book"). Next, Elan performed a series of studies designed to investigate the effects of food, age, and gender on the bioavailability of Skelaxin. The results of these studies, which are referred to as Studies 101, 103, 105, 106, and the meta-analysis, are detailed in King's prior submissions.

On June 20, 2002, and August 30, 2002, the FDA approved labeling revisions submitted by Elan to incorporate the results of Studies 101 (NDA 13-217/S-044) and 103 (NDA 13-217/S-036). On April 21, 2003, Elan submitted another labeling supplement to incorporate the results

of Studies 105, 106, and the meta-analysis (NDA 13-217/S-047). On June 12, 2003, King acquired Skelaxin from Elan and immediately began working with the FDA on the new labeling supplement. On March 12, 2004, the FDA Division of Anti-Inflammatory, Analgesic and Opthalmic Drug products in the Office of Drug Evaluation ("the Division") sent King a letter designating this labeling supplement as "approvable," pending a change in format to comply with the general ADME layout currently used in new product labels.

On April 5, 2004, King submitted further revised labeling that incorporated the results from all the studies in the requested ADME format and included important new information concerning the interrelationship of the effects of food, age, and gender on the bioavailability of Skelaxin. On October 6, 2004, the Division sent King another letter recommending additional revisions to the labeling based on safety considerations related to the new pharmacokinetic information.

On October 14, 2004 and October 22, 2004, King submitted letters acknowledging the safety issues raised by the Division and requesting an "end of review" conference to discuss "how this information should properly be conveyed." The Division agreed, and a meeting was held on December 10, 2004.

On April 22, 2005, as a result of the safety issues discussed with the FDA at the December 10, 2004 meeting, King submitted further revised labeling incorporating the Division's direction to include additional information about the pharmacokinetics in the PRECAUTIONS section of the label.

On August 14, 2006, the Division sent King another letter requiring further changes and specifically revising the proposed statement in the Precaution section to read as follows: "Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients sections.)"

On October 5, 2006, King submitted further revised labeling incorporating all requested revisions, including the specified revision to the Precaution section. On November 24, 2006, the FDA granted final approval of the Skelaxin labeling supplement. *See* Letter from Rappaport to King, S-046 (November 24, 2006) (copy attached as Exhibit A).

Thus, the new Skelaxin labeling is the product of over three years of consultation with the FDA and reflects substantial and significant revisions. It includes a substantially revised Clinical Pharmacology section that incorporates all currently available information relating to the food, age, and gender effects, as well as the interrelationship thereof. *See id.* Furthermore, the new Skelaxin labeling includes a new Precaution section that incorporates additional safety information as directed by the FDA and that specifically cross-references the portion of the Clinical Pharmacology section detailing the pharmacokinetics of Skelaxin and the interrelated effects of food, age and gender. *See id.*

C. Resubmission of Patent Listing Information

On December 21, 2006, following approval of the Skelaxin labeling supplement and according to FDA regulations, King resubmitted the Skelaxin patent information using FDA's

new patent declaration Forms 3542. *See* Letter from Rogers to Center for Drug Evaluation and Research, NDA 13-217 (December 21, 2006) (copy attached as Exhibit B). Pursuant to FDA regulations, these declarations identify the language found in the new Skelaxin labeling that corresponds to the methods of use claimed in the '128 and '102 patents, including the Clinical Pharmacology, Precautions, Indications and Usage, and Dosage and Administration sections. *Id.*

II. THE MARCH 1, 2004 LETTER IS NO LONGER APPLICABLE

In light of the new Skelaxin labeling, the March 1, 2004 Letter is no longer applicable to the carve-out issue. Specifically, the March 1, 2004 Letter addressed only the narrow issue of whether or not generic metaxalone applicants should be allowed to omit language related to "the fed-state bioavailability information" contained in the Skelaxin labeling that was in effect at the time. The issue of whether or not generic metaxalone applicants should be allowed to carve out information from the new Skelaxin labeling has not been addressed.

Moreover, the analysis of the carve-out issue is necessarily very different in light of the new Skelaxin labeling, which includes new information on the age and gender effects, their interrelationship with the food effect, and the safety information added to the labeling at FDA's request relating to the food effect of the drug. For example, the March 1, 2004 Letter specifically noted that the bioavailability data from Study 101 did not "result in any changes to the warnings, precautions or contraindications in the Skelaxin labeling." *See* March 1, 2004 Letter. Simply put, that statement is no longer true.

Likewise, the March 1, 2004 Letter addressed only the narrow issue of whether or not a section viii statement was appropriate to the '128 patent. As explained above, however, King recently submitted new patent information for Skelaxin using FDA's new patent listing Forms 3542. The issue of whether or not generic metaxalone applicants should be allowed to submit section viii statements to the '128 or '102 patents in light of King's recent declarations has not been addressed.

III. APPLICANTS SHOULD NOT BE ALLOWED TO CARVE-OUT INFORMATION FROM THE NEW SKELAXIN LABEL

To obtain approval of an Abbreviated New Drug Application ("ANDA"), a generic applicant must show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD, "except for changes required...because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). *See also* 21 U.S.C. § 355(j)(4)(G). Furthermore, FDA regulations narrowly define the acceptable variation between the two labels, which is limited to "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 21 C.F.R. § 314.94(a)(8)(iv)[2]. Moreover, FDA has repeatedly emphasized that "the exceptions to the

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[2] The reference in this regulation to differences in "bioavailability or pharmacokinetics" between the RLD and generic labeling applies only when the generic product has different bioavailability or

requirement of 'same labeling' are limited." Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, at 2881 (July 10, 1989) ("Consistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products or might create omissions of significant information."). Finally, FDA regulations provide that approval of an ANDA that omits an "aspect of labeling protected by patent" is conditioned on a finding by the FDA that the "differences do not render the proposed drug product ***less safe or effective*** than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7) (emphasis added).

Thus, a carve-out of information from the new Skelaxin labeling is contingent upon a finding by the FDA that generic metaxalone products will not be rendered ***any*** less safe or effective for the single condition of use remaining in the labeling. Notably, 21 C.F.R. § 314.127(a)(7) reads "***less*** safe or effective," not "unsafe or ineffective." Therefore, the standard is not whether carved-out labeling is ***adequate*** for the safe and effective use of generic metaxalone products. Rather, FDA regulations are clear that omission of information is not appropriate if the safety and efficacy of those products will ***in any way*** be affected by omission of the information in question. As explained in detail below, a carve-out of any information from the Clinical Pharmacology or Precaution sections of the new Skelaxin labeling would render generic metaxalone products less safe and effective than Skelaxin. First, the rationale

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pharmacokinetics than the RLD. *See, e.g.*, 21 C.F.R. § 320.1(e). It does not contemplate omission of pharmacokinetic information.

underlying the March 1, 2004 Letter was never appropriate and certainly does not apply to the new Skelaxin labeling. Second, the pharmacokinetic information relating to the food, age, and gender effects is essential to the safe and effective administration of the drug.

A. The Rationale Underlying the March 1, 2004 Letter Does Not Apply to the New Skelaxin Labeling

In the March 1, 2004 Letter, the FDA relied on essentially three arguments to support its conclusion that omission of food effect information was appropriate. None of these arguments apply to the new Skelaxin labeling.

First, the FDA stated:

> Because the clinical effect of the increased bioavailability is unknown, omission of fed-state bioavailability information from the labeling will not render the drug less safe for its approved uses. There are no data to support an increase in adverse events related to increased drug concentrations. Even if it were reasonable to conclude that increased bioavailability relates to an increase in adverse events, the labeling already adequately addresses the primary CNS (central nervous system) adverse events by way of the caution that "SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants." This caution applies to use of metaxalone without reference to the conditions of administration.

See March 1, 2004 Letter. This rationale was never appropriate and, as recognized by the FDA, should not apply to the new Skelaxin labeling. Specifically, on August 14, 2006, the Division sent King a letter requiring an addition to the Precaution section to read as follows: "Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients sections.)" Thus, the new Skelaxin labeling directly

links increased bioavailability in the fed state with increased CNS effects. Moreover, the Precaution section additionally draws this relationship in the context of a specific "condition of administration," *i.e.* administration of the drug with food. Further, the Precaution section now specifically cross-references the pharmacokinetics information in the Clinical Pharmacology section of the labeling, which relates to the increased bioavailability of the drug when taken with food. Thus, it can no longer be said that omission of information related to the food and age effects from either the Precaution or the Clinical Pharmacology sections of the labeling will not render the drug less safe. The general caution statement from the Information for Patients section quoted by the FDA does not address any of these specific concerns, which are only addressed in the Precaution and Clinical Pharmacology sections.

Second, the FDA explained:

> The Skelaxin labeling provides no information that links variations in bioavailability to the effectiveness of the drug. In fact, as noted above, the approved labeling specifically states that the clinical relevance of the food effect is unknown. Thus, because the clinical effect of increased bioavailability is unknown, omission of information on this characteristic of the drug will not affect the effective use of metaxalone.

See March 1, 2004 Letter. Again, this rationale was inappropriate for the old Skelaxin labeling and certainly cannot apply to the new Skelaxin labeling. The Precaution section now draws a direct link between increased bioavailability and enhancement of general CNS depression, which, as indicated in the Mechanism of Action section, is the likely mode of action of this drug. Moreover, the statement that the "clinical relevance of these effects is unknown" has been completely removed from the new Skelaxin labeling.

Finally, in the March 1, 2004 Letter, the FDA states:

> FDA notes that metaxalone has a long history of safe use. It has been marketed for decades without dosing adjustment information related to fed-state administration. Few adverse event reports have been entered into the Adverse Event Reporting System. Based upon the data available to the agency, there is no reason to believe that metaxalone will not continue to be safe and effective for use as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions.

See March 1, 2004 Letter. Again, this rationale was unsound as applied to the old Skelaxin labeling and should not apply to the new Skelaxin labeling, which incorporates new data that necessarily affects the safe administration of the drug. In fact, it was the Division that suggested that, based upon all available data, there is now reason to believe that the food effect is relevant to the safe use of the drug. Specifically, after the December 10, 2004 meeting between the Division and King, the Division circulated Meeting Minutes in which the FDA stated:

> Based on the results of the food effect, we know two things, that food increases C_{max} and prolongs T_{max}. The C_{max} increases to the largest extent in the youngest population studied, followed by the oldest and then the more middle age group. T_{max} increases substantially in the two older age groups in the fed state. For a drug to be dosed three to four times a day, a T_{max} of 6 or 8 hours is very problematic. This suggests onset of effect may be quite delayed resulting in early redosing, and as such, is a safety concern.

Thus, there can be no doubt, as recognized by the FDA, that the new information on the effects of food, age, and gender, as presented in the new Skelaxin labeling, is directly related to the safe administration of the drug.

B. Omission Of Information Relating to the Food, Age, or Gender Effects Would Render Generic Metaxalone Products Less Safe And Effective than Skelaxin

As explained above, the new Skelaxin labeling incorporates information from Studies 101, 103, 105, 106, and a meta-analysis of the results of those studies. One of the conclusions drawn from these studies is that the pharmacokinetics of metaxalone are significantly more affected by age under fasted conditions than under fed conditions, with bioavailability under fasted conditions increasing with age. On the basis of this and other data relating to the effect of food on the bioavailability of Skelaxin, the FDA included the following statement in the new Precaution section: "Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients section)." Thus, the information in the new Skelaxin labeling relating to the pharmacokinetics of metaxalone directly and necessarily affects the safe and effective prescribing and use of the drug for its single approved indication. Accordingly, such information cannot be omitted from generic metaxalone labeling without rendering such products less safe than Skelaxin for the labeled conditions of use of the drug.

As explained in the King Petitions and related submissions, it is King's belief that the pharmacokinetic information from the previous Skelaxin labeling was itself vital to the safe and effective use of the drug. The pharmacokinetic information in the new Skelaxin labeling, which includes new information on the age and gender effects, their interrelationship with the food

effect, and the safety issue raised by the FDA, is even more essential to the safe and effective administration of the product. *See* Elia Decl., ¶¶ 8, 28; Benet Decl., ¶¶ 10, 29, 31 (attached to the King Petitions as Exhibits 7 and 10). It is essential that, when prescribing drugs to patients, physicians are aware of conditions that may have a significant effect on bioavailability, including the effects of food, age, and gender – particularly the effects of food, which can be the source of variability within individual patients. This information is critical to predicting drug plasma levels, which, in turn, is critical in deciding how a drug should be administered to a specific patient. Lack of information about the variables that affect drug bioavailability can lead to problems with patient safety and treatment efficacy. Elia Decl., ¶ 10. For example, unexpected or unpredictable changes in a drug's bioavailability can lead to complications involving both the treatment of a patient and the patient's overall health. Elia Decl., ¶¶ 12, 14. In particular, when bioavailability of a drug is greater than expected under specific conditions, a potential safety risk can be created for the patient, unless the treatment regimen is adjusted accordingly or the patient is otherwise instructed regarding safe use under different conditions. Moreover, fluctuations in bioavailability can hinder a physician's determination of the most effective administration for a particular patient under certain conditions, unless sufficient information is provided to help identify and understand the causes and effects of those fluctuations. Elia Decl., ¶ 12. Indeed, the FDA seems to have recognized this point when it explained in the Meeting Minutes for the December 10, 2004 meeting that the interrelationship between the age and food effects "suggests onset of effect may be quite delayed resulting in early redosing, and as such, is a safety concern."

If the information on food, age, and gender effects, and the interrelationship thereof, were omitted from metaxalone labeling (whether brand or generic), a physician would conclude either that the bioavailability of metaxalone is unchanged when co-administered with food, in either male or female patients, young or old, or that the effects of food, age, and gender are unknown. Either of these conclusions would adversely affect the safe and effective administration of the drug, because they would be manifestly incorrect. If the physician concludes that the bioavailability of metaxalone is not affected by food, age, or gender, the physician will also conclude that adjustment of the treatment regimen is not necessary in any given sub-population. Alternatively, if the conclusion is that the effects are unknown, the physician will be left to "guess" as to the proper administration of the drug. In either case, omission of this information from the label deprives physicians of readily-available study data that are critical to the safe and effective administration of the drug. Elia Decl. ¶ 18.[3]

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[3] Furthermore, the FDA's recent decision concerning generic oxandrolone products (Docket No. 2005P-0383/CP1 and SUP1) ("Oxandrin Decision") supports King's position. In the Oxandrin Decision, the FDA concluded that the omitted labeling information merely provided geriatric-specific detail with respect to general information provided elsewhere in the labeling, which was not the subject of a carve-out and which was deemed adequate by the FDA to convey the information necessary for the safe and effective use of the drug. Thus, FDA stated that its determination to permit the omission of this geriatric labeling was "based on the determination that the labeling for generic oxandrolone would still contain adequate information to permit appropriate use and to minimize risks in all adults, including the geriatric population, with regard to each of the safety considerations also identified in the new geriatric labeling." Oxandrin Decision, at 14. Unlike Oxandrin, the information in the new Skelaxin labeling is part of the general information ***every*** prescriber and patient needs for the safe and effective use of the drug. An omission of this information would require, in the language of the Oxandrin Decision, a conclusion that the new Skelaxin labeling "contain[s] adequate information to permit appropriate use and to minimize risks in all adults," wholly apart from the information found in the Clinical Pharmacology and Precaution sections of the revised labeling. The new Skelaxin labeling simply does not provide this critical information anywhere else in the labeling.

IV. GENERIC METAXALONE APPLICANTS SHOULD BE REQUIRED TO SUBMIT PATENT CERTIFICATIONS PURSUANT TO 21 U.S.C. § 355(j)(2)(A)(vii)

As acknowledged by OGD in the March 1, 2004 Letter, a section viii statement is only appropriate if the method of use patent listed against the RLD "does not claim a use for which the [generic] applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). Moreover, FDA regulations further clarify that a section viii statement is only appropriate if "the labeling for the [generic] drug product...does not include any indications that are covered by the use patent." 21 C.F.R. § 314.94(a)(12)(iii). Rather, "[i]f the labeling of the [generic] drug product...includes an indication that, according to the patent information submitted under section 505(b) or (c) of the act and § 314.53...is claimed by a use patent," the generic drug applicant must file a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii). Furthermore, the FDA has provided a detailed explanation of the process and appropriate circumstances for submission of a section viii statement in its recent amendments to 21 C.F.R. § 314. *See* 68 Fed. Reg. 117 (June 18, 2003) ("the Final Rule"). Under these circumstances, the Final Rule and related FDA regulations are clear that generic metaxalone applicants should not be permitted to file a section viii statement.

In the preamble to the Final Rule, the FDA explained:

> We have modified the required declaration relating to method-of-use patents submitted.... The declarant must describe each individual method of use for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use.

Id. at 25-26. As described above, King has followed the procedure set out by the FDA and recently submitted the Skelaxin patent information on declaration Forms 3542. As required by the Final Rule and related FDA regulations, those declarations identify the language found in the new Skelaxin labeling corresponding to the methods of use claimed by the '128 and '102 patents. Specifically, the methods of use claimed by the '128 and '102 patents correspond to the Clinical Pharmacology, Indications and Usage, Precautions, and Dosage and Administration sections. *See* Letter from Rogers to Center for Drug Evaluation and Research, NDA 13-217 (December 21, 2006) (copy attached as Exhibit B).

In the Final Rule, the FDA further explains:

> In determining whether an ANDA applicant can "carve out" the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.
>
> * * *
>
> Our position has been that, for an ANDA applicant to file a section viii statement, it must "carve out" from the proposed ANDA labeling, the labeling protected by the listed patent. Unless the ANDA applicant can show that it is carving out certain method-of-use labeling, a section viii statement is not a correct submission for the listed patent.

Id. at 26-30. Thus, the Final Rule and related FDA regulations are clear that a section viii statement is only appropriate if the generic drug applicant is allowed to, and chooses to, carve out the ***entirety*** of the method of use information that the NDA holder declares is covered by the patents listed in the Orange Book. In the case of generic metaxalone products, this means that a section viii statement should only be allowed if generic metaxalone applicants are allowed to,

and choose to, carve out ***all*** of the new Skelaxin labeling language that King has declared is covered by the '128 and '102 patents – the entirety of the Clinical Pharmacology, Indications and Usage, Precautions, and Dosage and Administration sections. Because a carve-out of any of this information, much less all of it, would render generic metaxalone products less safe and effective than Skelaxin, the FDA should not accept section viii statements from generic metaxalone applicants.

V. GENERIC APPLICANTS SHOULD BE REQUIRED TO SUBMIT PROPOSALS TO THIS DOCKET IF THEY WISH TO CARVE OUT INFORMATION FROM THE NEW SKELAXIN LABELING OR FILE A SECTION viii STATEMENT

It is well-established that applicants have the burden of proof to establish their drug products' eligibility for approval. Thus, to justify omitting any information from their generic metaxalone labeling, generic metaxalone applicants have the burden of demonstrating that removal of such information would not render their generic metaxalone products less safe or effective for their labeled conditions of use. *See* 21 C.F.R. § 12.87(d) ("At a hearing involving issuing, amending, or revoking a regulation or order relating to the safety or effectiveness of a drug, device, food additive, or color additive, the participant who is contending that the product is safe or effective or both and who is requesting approval or contesting withdrawal of approval has the burden of proof in establishing safety or effectiveness or both and thus the right to approval"); 5 U.S.C. § 556(d) (1996) ("Except as otherwise provided by statute, the proponent of a rule or order has the burden of proof."). Until generic metaxalone applicants meet this burden,

they should not be permitted to omit any information from the generic metaxalone labeling or file section viii statements.[4] To King's knowledge, the FDA has never permitted an ANDA applicant to carve out labeling information pertaining to the pharmacokinetics of a drug in oral administration when the generic drug would nevertheless be indicated for oral administration. To the contrary, even when available pharmacokinetics information pertains to dosage forms or strengths which the applicant does not propose to sell (and cannot sell because of exclusivity restrictions), FDA has required generic labeling to include all pharmacokinetic information that appears in the labeling of the RLD. *See, e.,g.,* Package Insert for Teva Pharmaceutical Industries Ltd.'s 80 mg oxycodone hydrochloride extended release tablets, approved by FDA on March 23, 2004. *See also* 21 U.S.C. § 355(j)(2)(A)(v); 5 U.S.C. § 556(d); 21 C.F.R. § 12.87(d); Elia Decl.; Benet Decl. Thus, because the propriety of omission of any information from generic metaxalone labeling is currently the subject of this Docket, generic metaxalone applicants that rely on Skelaxin as the RLD should be required to submit proposals and new analyses to this Docket for comment by King, other generic manufacturers, and the public, if they wish to omit from their generic metaxalone labeling any information that appears in the new Skelaxin labeling or to file section viii statements.

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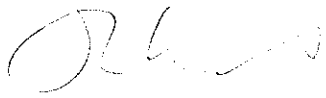
[4] In this regard, the requirements of the Hatch-Waxman Amendments are in full accord. Under 21 U.S.C. §355(j)(2)(A)(v), ANDA applicants have the burden of establishing that they propose to use the same labeling as was approved for the RLD and, thus, also to prove that any deviations therefrom fall within the limited exceptions to that requirement. This necessarily includes proof that the deviations they propose do not compromise the safety and efficacy of the drug.

VI. CONCLUSION

Based on the foregoing, the Commissioner is requested to: (a) prohibit the removal from generic metaxalone labeling of any information that appears in the revised Skelaxin labeling and (b) require applicants seeking approval to market generic metaxalone products that rely on Skelaxin as the RLD to submit a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) to the '128 and '102 patents.

Respectfully submitted,



Peter R. Mathers
Stacy L. Ehrlich
Jennifer A. Davidson
KLEINFELD, KAPLAN AND BECKER, LLP
1140 19th Street, NW
Washington, DC 20036
202-223-5120

Counsel for King Pharmaceuticals, Inc.